

Table S2. Novel substitutions found in L2 enzymes from clinical isolates.

Variant	Novel substitutions
L2_168_C6	Ser/Gly15Val, Ala/Lys16Pro, Ile/Ser/Asn20Thr, Pro/Ala21Ser, Thr47Ala, Lys/Ala100Gln, Glu/Gly140Asp, Val/Leu169Met, Thr/Ala257Pro, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_B9	Ser/Gly15Ala, Ala/Lys16Pro, Ile/Ser/Asn20Thr, His/Thr79Asn, Thr126Ala, Thr129Ile, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_G2	Ser/Gly15Ala, Ala/Lys16Pro, Ile/Ser/Asn20Thr, His/Thr79Asn, Pro96Ser, Thr126Ala, Thr129Ile, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_G2	Ala/Lys16Pro, Pro/Ala21Ser, Gly/Ala29Asp, Asp116Gly, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_E9	Ala/Lys16Pro, Ile/Ser/Asn20Leu, Pro/Ala21Ser, Gly/Ala29Asp, Ala208Thr, Ala/Pro258Val, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_F7	Ala/Lys16Pro, Pro/Ala21Ser, Ala208Thr, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_D7	Ser/Gly15Ala, Ala/Lys16Pro, Ile/Ser/Asn20Thr, Ala/Pro22Thr, Leu103Gln, Lys174Gln, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_F5	Ser/Gly15Ala, Ala/Lys16Pro, Ile/Ser/Asn20Thr, Lys/Ala100Gln, Glu/Gly140Asp, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_C8	Ala/Lys16Pro, Ala/Thr23-, Asn/Asp24-, Ala25-, Met/Val75Leu, Ala173Val, Ly227Thr, Ala254Gly, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_C5	Ala/Lys16Pro, Ala/Thr23-, Asn/Asp24-, Ala25-, Met/Val75Leu, Gly/Asp/Glu99Ala, Ala173Val, Ly227Thr, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_C2	Ala/Lys16Pro, Ala/Thr23-, Asn/Asp24-, Ala25-, Met/Val75Leu, Gly/Asp/Glu99Ala, Ala173Val, Ly227Thr, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_C9	Ala/Lys16Pro, Ala/Thr23-, Asn/Asp24-, Ala25-, Gly42Ser, Met/Val75Leu, Ala173Val, Ly227Thr, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_D6	Ala/Lys16Pro, Ala/Thr23-, Asn/Asp24-, Ala25-, Met/Val75Leu, Ala173Val, Ly227Thr, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_F8	Ala/Lys16Pro, Met/Val75Leu, Ala173Val, Ser/Thr182Gly, Ly227Thr, Ala/Pro258Val, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,

Variant	Novel substitutions
L2_167_A1	Ala/Lys16Pro, Pro/Ala21Leu, Met/Val75Leu, Ala173Val, Ly227Thr, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_B4	Ala/Lys16Pro, Ala/Pro22Val, Met/Val75Leu, Gly/Asp/Glu99Ala, Ala173Val, Ly227Thr, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_168_D4	Gly/-58Asp, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_I4	Ser82Gly, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_F3	Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_D4	Ala/Thr109Val, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_D1	Arg230Trp, Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_F7	Gln281Arg, Arg284Ala, Ile285Leu, Arg288Ala,
L2_167_C2	Ile/Ser/Asn20Arg, Asn/Asp24Glu, Gly/Ala29Thr, Ala/Thr/Ser31Asn, Lys38Met, Ile57Leu, Ser104Thr, Lys174Glu, Thr/Ala188Met, Asn/Glu197Asp, Ala208Ser, His/Val253Leu, Ala254S, Asp/Tyr272Asn, Ala/Thr/Ser277Gly,
L2_167_C1	Ile/Ser/Asn20Arg, Asn/Asp24Glu, Gly/Ala29Thr, Ala/Thr/Ser31Asn, Lys38Met, Ile57Leu, Gly/Arg/Gln/Met87Ala, Leu/Ile127Val, Val/Leu169Met, Lys174Glu, Asn/Glu197Asp, Ala208Ser, His/Val253Leu, Ala254S, Ala/Gly268Ser, Asp/Tyr272Asn, Ala/Thr/Ser277Gly,
L2_168_G4	Ile/Ser/Asn20Arg, Asn/Asp24Glu, Gly/Ala29Thr, Ala/Thr/Ser31Asn, Lys38Met, Ile57Leu, Gly/Arg/Gln/Met87Ala, Val95Met, Leu/Ile127Val, Val/Leu169Met, Lys174Glu, Asn/Glu197Asp, Ala208Ser, His/Val253Leu, Ala254S, Ala/Gly268Ser, Asp/Tyr272Asn, Ala/Thr/Ser277Gly,
L2_168_C1	Ala26Thr, Ile57Phe, Gly/Arg/Gln/Met87Thr, Lys174Glu, Thr/Ala188Met, Ala/Val194Gly, Val/Leu195Met, Gln200Lys, His/Val253Leu,
L2_168_A3	Ala26Thr, Ile57Phe, Gly/Arg/Gln/Met87Thr, Asp92Gly, Lys174Glu, His/Val253Leu, Ala/Gly268Ser, Arg275Gln, Ala/Thr/Ser277Val, Gly291Gln,
L2_167_B3	His/Val253Leu, Asp/Tyr272Asn,
L2_167_B8	Gly/Ala19Arg, Ile/Ser/Ans20Ala, Pro/Ala21Thr, Asn/Asp24Glu, Thr47Ser, Thr51Val, Ile57Ala, Gly/Arg/Gln/Met87Ala, Glu/Gly140Ala, Lys174Glu, Thr/Ala188Val, Ala/Thr/Ser277Met,

Variant	Novel substitutions
L2_167_H7	Ile/Ser/Ans20Ala, Ile57Val, Gly/Arg/Gln/Met87Thr, Val/Ala89Ser, Leu/Ile127Val, Val/Leu169Met, Lys174Glu, Thr/Ala188Gly, Asn/Glu197Lys, His/Val253Arg, Asp/Tyr272Asn, A/T/S277L,
L2_167_G9	Ala/Lys16Val, Ile/Ser/Ans20Ala, Ile57Val, Gly/Arg/Gln/Met87Thr, Val/Ala89Ser,
L2_167_G6b	Arg56Leu, Gly/Arg/Gln/Met87Thr,
L2_167_E2	Ala/Pro22Ser,
L2_168_C9	Ala/Pro22Ser, Gly42Glu,
L2_168_G1	Ser82Asn, Arg178His, Ala202Val,
L2_168_B1	Gly/Ala125Thr, Ala/Gly268Arg,
L2_167_I2	Gly59Ser, Val108Ile,
L2_167_A2	Gly59Ser,
L2_167_B2	Gly59Ser, Asp/Ser271Asn,
L2_167_G3	Ala/Val194Met,
L2_167_B5	Thr/Ala257Val,
L2_167_A4	Gly/Arg/Gln/Met87Thr,